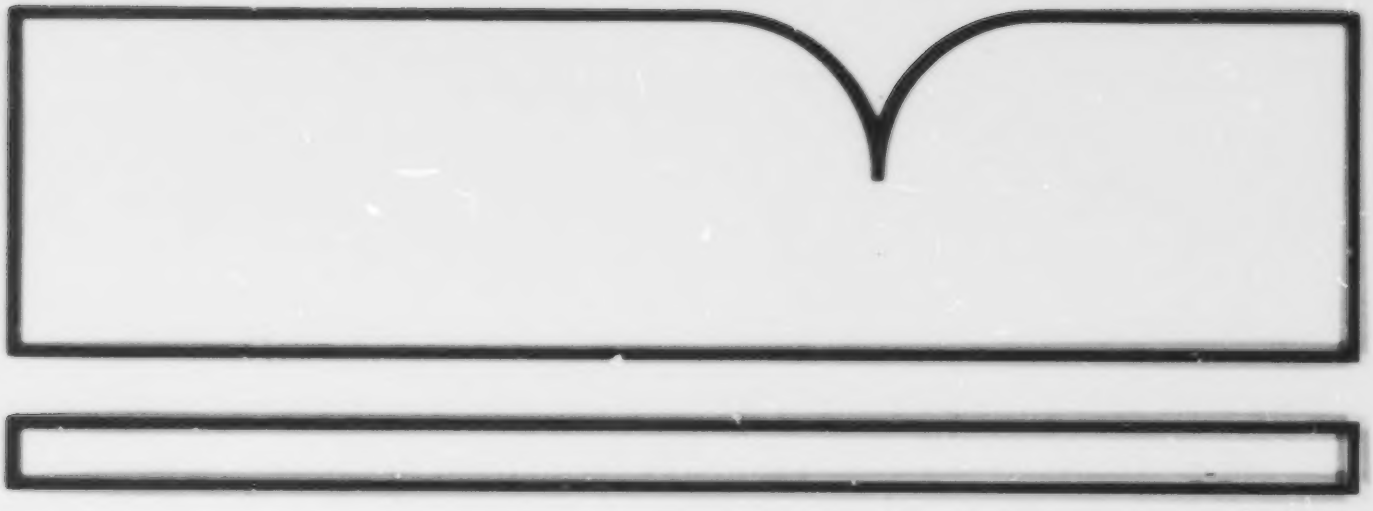
PB88-218789

Health and Environmental Effects Profile for Carbazole

(U.S.) Environmental Protection Agency
Cincinnati, OH

Apr 86



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TECHNICAL REPORT DATA
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1. REPORT NO. EPA/600/X-86/334	2.
3. RECIPIENT'S ACCESSION NO. PB88-218789/AS	
4. TITLE AND SUBTITLE: Health and Environmental Effects Profile for Carbazole	5. REPORT DATE: April 1986
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS: Environmental Criteria and Assessment Office, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE: EPA/600/22
15. SUPPLEMENTARY NOTES	

16. ABSTRACT

The Health and Environmental Effects Profile for Carbazole was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Carbazole has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for carbazole is 2.08×10^{-2} $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT: Public	19. SECURITY CLASS (This Report): Unclassified	21. NO. OF PAGES: 67
	20. SECURITY CLASS (This page): Unclassified	22. PRICE: A04 $14.95

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB88-218789
EPA/600/X-86/334
April 1986

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CARBAZOLE

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REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
SPRINGFIELD, VA. 22161

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

Carbazole is a PAH produced in the United States as a constituent (<1%) of coal tar (McNeil, 1983), which is produced in large quantities by the steel industry as a by-product of coke manufacture (USITC, 1984a). Refined carbazole, as an end-use product, is not made in the United States (IARC, 1983), but it is imported. About 0.416 million pounds of refined carbazole were imported into the United States in 1983 (USITC, 1984b). Refined carbazole is used in the synthesis of dyes and other chemicals, as an odor inhibitor in detergents, and to make photographic plates sensitive to UV light (Windholz, 1983; Hort and Waxman, 1983; Hawley, 1981). Coal tar is used in creosote wood preservatives and anticorrosion coatings, as a feedstock for carbon-black manufacture, and as a binder for road surfacings and electrodes (McNeil, 1983).

The major source by which carbazole is emitted to the aquatic and atmospheric environments appears to be in emissions and releases from the coal tar industry and the coal tar use industries. Carbazole has been detected in groundwaters apparently contaminated by these industries (Ehrlich et al., 1982; Wilson et al., 1983), in coal-conversion wastewaters (Singer et al., 1978), in air emissions from coking operations (York Research Corp., 1979) and in coal tar pitch fumes (Verschueren, 1983). Carbazole has been found in drinking waters (Kveseth et al., 1982; Fielding et al., 1981) and in the ambient air of various cities and countries (Schuetzle et al., 1975; Daisey and Leyko, 1979; Thrane and Mikalsen, 1981). Carbazole occurs as a product of incomplete combustion of nitrogen-containing organic matter (IARC, 1983) and has been found in stack emissions from waste incineration (Junk and Ford, 1980).

Experimental studies conducted by Smith et al. (1978) have shown photolysis and biodegradation to be the dominant fate processes in the removal of carbazole from the aquatic environment. The photolytic half-life near the water's surface in winter was ~3 hours. Aquatic hydrolysis, oxidation and volatilization are not environmentally significant. The BCF for carbazole, experimentally measured in a variety of aquatic organisms, ranges from 44-125 (Southworth et al., 1979; Lu et al., 1978), indicating that bioaccumulation is not likely to be important.

Carbazole is expected to rapidly photolyze in sunlit atmospheres based on its strong UV absorption (Sadtler, 1968) and rapid photolytic degradation in water (Smith et al., 1978). The National Research Council (1983) has suggested that atmospheric reaction with hydroxyl radicals, ozone, sulfur dioxide or nitrogen dioxide may be important removal mechanisms for PAHs, such as carbazole; however, experimental data confirming this hypothesis have not been reported. The detection of carbazole in airborne particulate matter (Daisey and Leyko, 1979) and in atmospheric aerosol (Schuetzle et al., 1975) suggests that absorption and dry deposition may be physical transport mechanisms, while carbazole in airborne particulates may be resistant to phototypes.

Carbazole has been shown to degrade, primarily by biodegradation; in a Russian soil at a half-life rate of 3-10.5 days under laboratory conditions, the rate constants were 0.231 and 0.067 day^{-1} for carbazole concentrations of 5 and 500 mg/kg, respectively, although, if present on moist soil, carbazole may be mobile, leaving little at the soil surface to be photolyzed (Medvedev and Davydov, 1972). Photolysis of carbazole on soil surfaces is expected to occur because of its strong UV absorption. Experimental leaching studies (Smith et al., 1978) have shown carbazole to have a medium soil

mobility; the presence of carbazole in groundwaters (Ehrlich et al., 1982; Wilson et al., 1983) suggests that leaching does occur even though leaching estimation methods predict that carbazole will have slight or no soil mobility.

Limited pharmacokinetic data from rats indicate that carbazole is incompletely (~70%) absorbed from the gastrointestinal tract, distributed throughout the body, metabolized primarily to 3-hydroxycarbazole and conjugated with glucuronic acid, and almost completely excreted in the urine within 24 hours; this is considered to be a rapid absorption and excretion in the rat (Hasegawa et al., 1985; Johns and Wright, 1964).

Administration of carbazole in the diet of B6C3F1 mice at concentrations of 0.15, 0.3 and 0.6% for 96 weeks produced significantly increased incidences of hepatocellular carcinomas (both sexes), squamous cell carcinomas of the forestomach (males) and related proliferative lesions (neoplastic nodules in the liver and forestomach papillomas in both sexes) (Isuda et al., 1982). Inadequately designed or reported subcutaneous injection (Shear and Leiter, 1941) and dermal application (Kennaway, 1924; Maisin et al., 1927; Shear and Leiter, 1941) studies with mice did not show local tumorigenic effects of carbazole. Supporting carcinogenesis evidence of carbazole derivatives has been reported in the past (Boyland et al., 1937, Lagassagne et al., 1961; Sellakumar et al., 1977).

The results of bacterial mutagenicity assays of carbazole (numerous Ames reverse mutation plate, assays with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and/or TA100, a reverse mutation assay with Escherichia coli Sd-4-73, a forward mutation assay with S. typhimurium TM677) were negative or, in the case of two Ames assays (a spot test with multiple strains and a plate test with strain TA98), equivocal. Inadequately reported studies indicate that carbazole was not differentially toxic to wild-type or

DNA-repair deficient strains of Bacillus subtilis, but did induce chromosomal aberrations in cultured Chinese hamster fibroblasts.

Carbazole derivatives can be pharmacologically active drugs in that they show (in different biological systems) antiviral, antiasthmatic, antiinflammatory and antidepressant activities. Although the rather high doses administered in the present B6C3F1 mice study cannot be rationalized at this time by any of these mechanisms, they should be considered when interpreting any of the biological effects of carbazole or carbazole derivatives.

Information regarding chronic toxic effects unrelated to carcinogenesis, subchronic toxicity, teratogenicity or other reproductive effects were not located in the available literature cited in the Appendix.

Concentrations of carbazole in water at $\geq$1 mg/l were acutely letnal to the saltwater fish, Mugil cephalus, while concentrations $\leq$0.1 mg/l were tolerated for 1 week (Thomas et al., 1981). A concentration of 5 mg/l was lethal to the freshwater fishes, Salmo gairdneri and Lepomis macrochirus (Applegate et al., 1957).

A q_{1H}^* of 2.08×10^{-2} $(mg/kg/day)^{-1}$ and an F factor of 9.23×10^{-2} $(mg/kg/day)^{-1}$ were estimated for risk assessment purposes based on carbazole-induced hepatocellular carcinomas in B6C3F1 male mice (Tsuda et al., 1982). It is recognized that males in this strain typically (historical average 21$\pm$6.5%) show a higher incidence of liver carcinomas than females. This F factor indicates that carbazole should be placed in potency group 4. Since carbazole is in potency group 4 and is most appropriately categorized in EPA category B2 (U.S. EPA, 1984), it has a LOW hazard ranking under CERCLA. Calculation of an RQ based on chronic toxicity for carbazole is precluded by the lack of appropriate (i.e., unrelated to carcinogenesis) chronic toxicity data and a lack of subchronic toxicity and teratology/fetotoxicity data.

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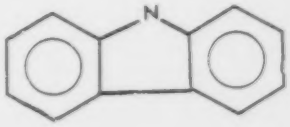
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CAS	Chemical abstract service
DNA	Deoxyribonucleic acid
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
PAH	Polycyclic aromatic hydrocarbons
ppb	Parts per billion
ppm	Parts per million
RQ	Reportable quantity
UV	Ultraviolet
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Carbazole is the common chemical name but this compound is also known as 9H-carbazole, 9-azafluorene, dibenzopyrrole, dibenzo(b,d)pyrrole and diphenylenimine. The structure, molecular weight, empirical formula and CAS Registry number for carbazole are as follows:



Molecular weight: 167.20

Molecular formula: $C_{12}H_9N$

The CAS Registry number for this compound is 86-74-8.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Carbazole is a white crystalline solid with a characteristic odor (Hawley, 1981). One gram of carbazole dissolves in 3 mℓ quinoline, 6 mℓ pyridine, 9 mℓ acetone, 35 mℓ ether, 120 mℓ benzene and 135 mℓ absolute alcohol. It is slightly soluble in petroleum ether, chlorinated hydrocarbons and acetic acid (Windholz, 1983). Selected physical properties are listed below:

Melting point:	244-246°C	Hawley, 1981
Boiling point	352-354°C	Hawley, 1981
Specific gravity (18/4°C):	1.10	Windholz, 1983
pKa:	approximately -3.0	Smith et al., 1978
Vapor pressure		
at 20°C	7.0×10^{-4} mm Hg (calculated)	Smith et al., 1978
at 248.2°C	60 mm Hg	Perry and Green, 1984
Water solubility:		
at 20°C	1.03 mg/ℓ	Smith et al., 1978
at 20-25°C	1.2 mg/ℓ	Pearlman et al., 1983
Log K_{ow}:	3.72	Hansch and Leo, 1981

The vapor pressure at 20°C was estimated by Smith et al. (1978) using experimental vapor pressure data obtained above the melting point of carbazole and applying the Clausius-Clapeyron equation.

Carbazole is an extremely weak base that reacts with potassium hydroxide to yield the N-potassium salt. It also reacts with nitrogen oxides (IARC, 1983), and in the presence of alkaline catalysts, reacts readily with acetylene (Hort, 1978).

1.3. PRODUCTION DATA

Carbazole is not manufactured in the United States as a refined end-use product (IARC, 1983); however, it is a constituent of coal tar (McNeil, 1983), which is produced chiefly by the steel industry as a by-product of coke manufacture (USITC, 1984a). In the United States, an average coke-oven tar contains 0.60% carbazole on a dry tar weight basis (McNeil, 1983). Coal tar production in the United States in 1983 amounted to 284 million gallons, as reported by 27 companies and their subsidiaries (USITC, 1984a). Carbazole is also a minor constituent of California crude petroleum (Elliott and Melchior, 1982).

Carbazole is manufactured as a refined end-use product in foreign countries. World demand for isolated carbazole is completely satisfied by feedstocks from coking operations that refine carbazole by distillation and extraction methods (Collin and Lohnert, 1984). Importation of refined carbazole into the United States through principal custom districts has been reported as follows (USITC, 1982, 1983, 1984b):

Year	Imports (millions of pounds)
1983	0.416
1982	0.104
1981	0.524

1.4. USE DATA

Carbazole is used as an intermediate in the manufacture of commercially important dyes (Windholz, 1983). It is also used commercially in the production of N-vinyl-carbazole, which is used to make rigid high-melting polymers (Hort, 1978; Hort and Waxman, 1983). Other reported uses for carbazole include manufacture of explosives, insecticides, lubricants and rubber antioxidants, and making photographic plates sensitive to UV light. It is also used as an odor inhibitor in detergents and as a reagent for lignin, carbohydrates and formaldehyde (Hawley, 1981; Windholz, 1983).

Coal tar, which contains carbazole as a constituent, is used in creosote wood preservatives and anticorrosion coatings, as a feedstock for carbon-black manufacture, and as a binder for road surfacings and electrodes (McNeil, 1983).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

Smith et al. (1978) estimated the pKa of carbazole to be approximately -3.0, indicating that carbazole would be present in the protonated form at <1% at pH 1, and that the environmental chemistry of carbazole would involve only the free base.

2.1.1. Hydrolysis. Carbazole contains no hydrolyzable groups (Smith et al., 1978); therefore, hydrolysis of carbazole in the aquatic environment is not expected to occur.

2.1.2. Oxidation. The alkyl peroxy radical ($RO_2\cdot$) is generated in natural bodies of water by sunlight by photochemical mechanisms (Mabey et al., 1981). The rate constant for a reaction between $RO_2\cdot$ and carbazole has been experimentally determined to be 29 M^{-1} sec^{-1} (Smith et al., 1978). The concentration of $RO_2\cdot$ in surface waters of sunlit bodies of water is ~10^{-9} M (Mabey et al., 1981). Therefore, the half-life of carbazole in water, with respect to $RO_2\cdot$ oxidation, is calculated to be 277 days; this rate is not competitive with photolysis or biodegradation in the environment.

2.1.3. Photolysis. Carbazole strongly absorbs UV light in the spectral region >290 nm (Sadtler, 1968), suggesting a potential for environmental photolysis. Smith et al. (1978) conducted aqueous photolysis studies with carbazole and found that carbazole readily photolyzed under environmental conditions. In initial tests, Smith et al. (1978) dissolved 1 ppm carbazole in either pure water, Lake Tahoe water, Coyote Creek water or Searsville pond water and irradiated the solutions with a 313 nm irradiation source; 1% acetonitrile was added to the solutions to increase the solubility of carbazole. The observed photolysis rate constants for these waters varied only slightly with a range of 5.74-7.69x10^{-5} sec^{-1} (half-life range of 3.35

to 2.50 hours). A similar test using humic acid in pure water produced a rate constant of $2.46 \times 10^{-5} sec^{-1}$ (half-life of 7.83 hours). First-order kinetic behavior was observed for the photolyses rates beyond two half-lives of carbazole. The retardation of photolysis with humic acid was thought to be caused by a screening effect that lowered the light intensity. In a test with carbazole in pure water exposed to sunlight during midday in late January, Smith et al. (1978) determined a photolysis rate constant of 6.59×10^{-5} sec^{-1} (half-life of 2.9 hours).

Smith et al. (1978) also used the method of Zepp and Cline (1977) to estimate the direct photolysis rate of carbazole in sunlight at 40° latitude using its quantum yield and measured absorption spectra data. The calculated half-life of 2.7 hours agrees with the measured value of 2.9 hours. Mill et al. (1981) used the data from Smith et al. (1978) and Zepp and Cline (1977) to estimate the seasonal variation in photolysis rates for carbazole at 40° latitude at noon. The half-lives during specified seasons are as follows:

Date	Half-life (hours)
December 21 (Winter)	2.96
March 21 (Spring)	1.93
June 21 (Summer)	0.96
September 21 (Fall)	2.14

These half-lives indicate that photolysis is rapid and also a major removal mechanism for carbazole in the aquatic environment.

2.1.4. **Microbial Degradation.** Smith et al. (1978) examined the biodegradability of carbazole in a series of laboratory tests and reported that biodegradation of carbazole probably occurs under a variety of environmental conditions. Carbazole was readily degraded in these unadapted enrichment culture tests using Coyote Creek water, Searsville Pond water and cultures

obtained from two sewage treatment plants and an oil refinery waste treatment plant; 60-99% of the carbazole was degraded with these inocula within 5-11 days of incubation. With adapted microorganisms, >90% biodegradation was observed in 24-48 hours. Biodegradation of carbazole did not occur, however, in Lake Tahoe water after 42 days of incubation. Based on their experimental results in a culture system developed from a sewage plant effluent, Smith et al. (1978) estimated the biodegradation rate constant to be 5×10^{-7} (ml cell^{-1} hour^{-1}).

Fedorak and Westlake (1984) used a mixed bacteria culture (enriched on carbazole) as seed to test the biodegradability of carbazole and the C_1-, C_2- and C_3-carbazoles present in the nitrogen-rich fraction of Norman Wells crude oil; the tests were conducted in a series of flasks containing a mineral water medium. Most of these carbazoles were completely degraded within 8 days.

The microbial studies discussed above suggest that biodegradation of carbazole in the aquatic environment is potentially an important removal mechanism in natural aquatic media other than oligotrophic lakes.

2.1.5. Volatilization. Smith and Bomberger (1980) used experimental methods to measure the ratio of the volatilization rate constant of carbazole to the oxygen reaeration rate constant and determined this ratio to be 0.0001. Using representative oxygen reaeration rates cited in Mabey et al. (1981), the following volatilization half-lives for carbazole are calculated:

	Oxygen Reaeration Rate (days^{-1})	Volatilization Half-Life (days)
Pond	0.19	36,500
River	0.96	7,220
Lake	0.24	28,900

These values indicate that volatilization is not environmentally important.

2.1.6. Adsorption. Smith et al. (1978) conducted aqueous adsorption tests with carbazole using Coyote Creek sediment and calcium montmorillonite clay as adsorption media. The K_{oc} values for the sediment and clay were determined to be 175 and 3.2, respectively, indicating that carbazole is not expected to be absorbed significantly in aquatic sediment. The adsorption-desorption process under heavy loading conditions, however, may increase the persistence times in natural waters (Smith et al., 1978).

2.1.7. Bioaccumulation. Southworth et al. (1979) experimentally measured the bioaccumulation of carbazole in Daphnia pulex using static-water laboratory conditions and measured a BCF of 115. Lu et al. (1978) used a model ecosystem and radio-labelled carbazole to measure the following BCFs in various aquatic organisms:

Organism	BCF
fish (Gambusia)	125
mosquito (Culex)	112
snail (Physa)	134
alga (Oedogonium)	44

Using the Japanese MITI test, Sasaki (1978) found carbazole to be nonbioaccumulative to low bioaccumulative.

These data indicate that bioaccumulation of carbazole in aquatic organisms is not important in relation to photolysis or biodegradation.

2.1.8. Other Fate Processes. Lin and Carlson (1984) examined the reaction of dilute aqueous solutions of hypochlorite/hypochlorous acid or chlorine dioxide with carbazole at free chlorine concentrations similar to that used during the chlorination step of drinking water treatment. The carbazole was found to react quite rapidly suggesting that raw waters containing carbazole are susceptible to chemical reaction if subjected to industrial or commercial chlorination treatment.

2.2. AIR

2.2.1. Chemical Removal Processes. Carbazole strongly absorbs UV light in the spectral region >290 nm (Sadtler, 1958), suggesting a potential for environmental photolysis. Smith et al. (1978) also reported that carbazole photolyzes readily in aqueous media. These data indicate that photolysis is probably a major removal fate mechanism in sunlit atmospheres.

Data specific to the atmospheric reaction of carbazole with hydroxyl or other radical species, with ozone or with NO_x and sulfur dioxide have not been reported. Based on limited experimental data, the NCR (1983) has suggested that photooxidation and reaction with oxidants, such as ozone and sulfur dioxide, may constitute a major pathway for the removal of PAHs from the atmosphere. Tokiwa et al. (1981) have shown experimentally that carbazole, adsorbed onto filter paper and exposed to 10 ppm nitrogen dioxide in the dark for 24 hours, reacts readily with nitrogen dioxide.

2.2.2. Physical Removal Processes. Carbazole has been detected in the atmospheric aerosol (Schuetzle et al., 1975) and as airborne particulate matter (Daisey and Leyko, 1979), suggesting that adsorption and subsequent precipitation may be important in the atmospheric fate of the compound. Kormacher et al. (1980) tested the ability of carbazole adsorbed to coal fly ash to oxidize in the dark, but the carbazole was found to be stable. In sunlight, however, it is likely that carbazole will react photochemically. The importance of carbazole removal from air by rainfall or dry deposition is not clear.

2.3. SOIL

2.3.1. Microbial Degradation. As reviewed by Sims and Overcash (1983), Medvedev and Davydov (1972) examined the rate of degradation of carbazole in a chernozem soil in laboratory studies. Using initial carbazole concentrations of 5 and 500 mg/kg, the authors determined the degradation rate

constants were 0.231 and 0.067 day^{-1} for carbazole concentrations of 5 and 500 mg/kg, respectively. While some surface photolysis may have occurred during this study, the degradation can probably be attributed to microbial means. As noted in Section 2.1.4., environmentally significant biodegradation of carbazole in natural pond and creek waters has been reported (Smith et al., 1978). These data suggest that biodegradation of carbazole in natural soil systems will be significant.

2.3.2. **Photolysis.** Environmentally rapid photolysis of carbazole in aquatic systems has been demonstrated (see Section 2.1.3.; Smith et al., 1978). It is therefore likely that photolysis will occur on the surface of natural soil systems; however, the importance of photolysis in soil is restricted to the amount of carbazole exposed to the surface of soil, since subsurface material will not be exposed to sunlight. Leaching of carbazole in moist soil will further remove carbazole from the soil surface, leaving little to be photolyzed.

2.3.3. **Adsorption/Leaching.** Smith et al. (1978) experimentally determined the K_{oc} values for carbazole in creek sediment and calcium montmorillonite to be 175 and 3.2, respectively (see Section 2.1.6.). A compound having a K_{oc} of 175 is classified as having medium mobility in soil (Swann et al., 1983).

These experimental results differ from the leaching predictions based on carbazole's WS (1.03 ppm), Log K_{ow} (3.72) and molecular topology. The following regression equations can be used to predict soil adsorption (Lyman et al., 1982):

$$\log K_{oc} = 3.64 - 0.55 \log WS \text{ (in ppm)} \qquad (2\text{-}1)$$

$$\log K_{oc} = 0.544 \log K_{ow} + 1.377 \qquad (2\text{-}2)$$

The K_{oc} values calculated from Equations 2-1 and 2-2 are 4300 and 2500, respectively, indicating slight soil mobility. Prediction of K_{oc} based on the molecular topology and quantitative structure analysis method of Sabljic (1984) yields a K_{oc} value of 9900, indicating immobility in soil.

Carbazole has been detected in several groundwaters (Section 3.1.), suggesting that under certain conditions it can leach in soil.

2.3.4. Volatilization. Based on its low vapor pressure of 7.0×10^{-4} mm Hg at 20°C (Smith et al., 1978) and its lack of volatility from water (see Section 2.1.5.) carbazole is not expected to volatilize significantly from soil.

2.4. SUMMARY

Based primarily on experimental studies conducted by Smith et al. (1978), photolysis and biodegradation are expected to be the dominant fate processes with respect to carbazole in the aquatic environment. The photolytic half-life at near-surface water in winter was ~3 hours. Hydrolysis, aquatic oxidation and volatilization are not environmentally important when compared with photolysis or biodegradation. Aquatic adsorption is also relatively insignificant; however, the adsorption-desorption mechanism may increase the persistence times of carbazole in natural waters (Smith et al., 1978). The BCF for carbazole in a variety of aquatic organisms has been experimentally measured to range from 44-125 (Southworth et al., 1979; Lu et al., 1978) indicating that bioaccumulation is relatively unimportant.

Carbazole is expected to rapidly photolyze in sunlit atmospheres based on its strong UV absorption (Sadtler, 1968) and rapid photolytic degradation in water (Smith et al., 1978). Reaction with hydroxyl radicals and other oxidants such as ozone, nitrogen oxides or sulfur dioxides may also be important atmospheric removal pathways for carbazole (NCR, 1983); however,

sufficient experimental data have not been generated to confirm this suggestion. Carbazole has been detected in airborne parti- culate matter and in atmospheric aerosol (Daisey and Leyko, 1979; Schuetzle et al., 1975) indicating that adsorption and subsequent precipitation may be significant transport mechanisms, while carbazole in airborne particulate may be resistant to photolysis..

Carbazole has been shown to degrade, primarily by biodegradation, in Russian soil under laboratory conditions; the rate constants were 0.231 and 0.067 day^{-1} for carbazole concentrations of 5 and 500 mg/kg, respectively (Medvedev and Davydov, 1972; Sims and Overcash, 1983). Photolysis of carbazole is expected to occur on soil surfaces. Experimental leaching studies (Smith et al., 1978) have shown that carbazole has a medium soil mobility, while leaching estimation methods predict carbazole to have slight or no mobility in soil. Volatilization of carbazole from soil is not likely to be significant.

3. EXPOSURE

3.1. WATER

Ehrlich et al. (1982) detected carbazole at a concentration of 24 mg/kg in aquifer thought to be contaminated by releases from a coal tar distillation and wood-treating plant in St. Louis Park, MN. Carbazole was identified (no concentration reported) in groundwaters contaminated by a waste lagoon at a wood creosote plant in East Texas (Wilson et al., 1983), in groundwater near a hazardous waste site near Pensacola, FL (Rostad et al., 1984) and in coal-conversion wastewaters (Singer et al., 1978).

Carbazole has been detected in tap water in Norway (Kveseth et al., 1982) and in two unidentified drinking water supplies in the United States (Fielding et al., 1981), but no concentrations were reported. Vassilaros et al. (1982) detected 110 ppb carbazole in a catfish sample taken from the Black River. The U.S. EPA Storet Data base lists only one unspecified observation for carbazole.

The major source of carbazole in the aquatic environment appears to be wastewater and other emissions generated by the coal tar and associated industries because carbazole is a component of coal tar (see Section 1.3.) and creosote, a coal tar product commonly used in wood preserving (McNeil, 1983).

3.2. FOOD

Pertinent data regarding the detection of carbazole in food were not located in the available literature cited in th Appendix.

3.3. INHALATION

Carbazole has been detected in air emissions from a coke quench tower at U.S. Steel Corporation's Lorain, OH plant (York Research Corp., 1979), in cigarette smoke (IARC, 1983; Snook et al., 1978) and in marijuana smoke (Zamir-ul et al., 1974). Carbazole occurs in the products of incomplete

combustion of nitrogen-containing organic matter (IARC, 1983) and has been found in stack emissions from waste incineration (Junk and Ford, 1980). Coal tar pitch fumes can contain 9.6 weight % carbazole plus methylphenanthrene (Verschueren, 1983).

Carbazole concentrations ranging from ~2-50 ng/m³ have been found in atmospheric aerosol samples collected in Pasadena, CA, during a period of atmospheric inversion (Schuetzle et al., 1975). Daisey and Leyko (1979) detected carbazole in air-borne particulate matter collected in New York City. Thrane and Mikalsen (1981) also detected carbazole in background, suburban and urban air samples collected in Norway.

Carbazole has been monitored in the work atmosphere at various occupational locations in Norway. Particulate concentrations as high as 19,000 ng/m³ and gaseous concentrations as high as 11,000 ng/m³ were monitored within a coke plant (Bjoerseth et al., 1978a). Typical particulate concentrations of 960 ng/m³ (maximum of 29,600 ng/m³) and gaseous levels reaching 200 ng/m³ were monitored within an aluminum reduction plant (Bjoerseth et al., 1978b, 1981); aluminum production involves heating carbonaceous electrode materials to 1000°C temperatures under which coal tar pitch volatiles and particulates may be released. A Norwegian carbon paste plant was found to contain particulate carbazole levels of 3900 ng/m³ (Bjoerseth and Lunde, 1977), while Gammage (1983) detected carbazole concentrations ranging from not detected to 12,900 ng/m³ at coal gasification and liquification pilot plants in the United States.

3.4. DERMAL

The most probable route of skin contamination from compounds produced by synfuel technologies is by occupational exposure to leakages or other contacts (Gammage, 1983). Monitoring data specifically for carbazole have not been reported.

3.5. SUMMARY

The major source by which carbazole is emitted to the aquatic and atmospheric environments appears to be in emissions and releases from the coal tar industry and the coal tar use industries. Carbazole has been detected in groundwaters apparently contaminated by these industries (Ehrlich et al., 1982; Wilson et al., 1983), in coal-conversion wastewaters (Singer et al., 1978) and in drinking waters (Kveseth et al., 1982; Fielding et al., 1981).

Air emissions from coking operations (York Research Corp., 1979) and coal tar pitch fumes (Verschueren, 1983) contain carbazole. Carbazole is an incomplete combustion product (IARC, 1983) that has been found in waste incineration emissions (Junk and Ford, 1980) and in cigarette and marijuana smoke (IARC, 1983; Zamir-ul et al., 1974). Carbazole has also been detected in the ambient air of various cities and countries at a concentration as high as 50 ng/m^3 (Schuetzle et al., 1975; Daisey and Leyko, 1979; Thrane and Mikalsen, 1981).

4. PHARMACOKINETICS

4.1. ABSORPTION

Information reported in an abstract of a Japanese study (Hasegawa et al., 1985) indicates that ~70 and 33% of the radioactivity of an unspecified oral dose of uniformly labeled ^{14}C-carbazole was eliminated in the urine and feces of female rats, respectively, in 24 hours. These data suggest that carbazole is substantially absorbed from the gastrointestinal tract.

4.2. DISTRIBUTION

Hasegawa et al. (1985) indicated that radioactivity from an unspecified oral dose of uniformly-labeled ^{14}C-carbazole was distributed to the liver, kidneys, adrenals, thyroid and brain of rats. The half-lives of the radioactivity in the liver, adrenals, thyroid and brain were reported to be 13.7, 12.4, 12 and 11.5 hours, respectively; a half-life for the kidneys was not reported.

4.3. METABOLISM

3-Hydroxycarbazole, conjugated with glucuronic acid, has been identified by paper and thin-layer chromatography as a urinary metabolite of carbazole in rats and rabbits (Johns and Wright, 1964). Six male albino rats that were administered single intraperitoneal doses of 4 mg/kg carbazole and one male albino rabbit that was administered 1 g carbazole by gavage were used in this study. The rat experiment involved administration of uniformly labeled ^{14}C-carbazole; the distribution of radioactivity during metabolite purification indicated that 3-hydroxycarbazole was the major urinary metabolite, comprising 60% of the extracted radioactivity. The structures of the other metabolites were not established, but reportedly probably included other phenolic compounds.

Hydroxycarbazole (not otherwise specified) was also reported to be the major urinary metabolite in female rats that were treated orally with uniformly labeled ^{14}C-carbazole (Hasegawa et al., 1985). Additional information regarding the design or results of this study were not reported in the abstract.

4.4. EXCRETION

Intraperitoneal injection of 4 mg/kg of uniformly labeled ^{14}C-carbazole into six male albino rats resulted in mean urinary elimination of 60, 3.5 and 0.5% of the administered radioactivity after 24, 48 and 72 hours, respectively (Johns and Wright, 1964).

Hasegawa et al. (1985) reported that ~70 and 33% of the administered radioactivity from an unspecified oral dose of uniformly labeled ^{14}C-carbazole was eliminated in the urine and feces, respectively, in 24 hours. The ^{14}C concentration in the gastrointestinal tract decreased to <1% of the administered dose in 24 hours, and a small unspecified discharge into the bile was observed.

4.5. SUMMARY

The limited pharmacokinetic data from rats indicate that carbazole is absorbed substantially (~70%) from the gastrointestinal tract, distributed throughout the body, metabolized primarily to 3-hydroxycarbazole and conjugated with glucuronic acid, and excreted mainly in the urine within 24 hours (Hasegawa et al., 1985; Johns and Wright, 1964). Such rapid metabolic processing as well as the conjugation at a 3-hydroxy site on carbazole in rodents is assumed to happen also in man.

5. EFFECTS

5.1. CARCINOGENICITY

In the only carcinogenicity study available in which carbazole was administered using a natural route of exposure, groups of 50 male and 50 female, 6-week-old B6C3F1 mice were fed diets containing 0, 0.15, 0.3 or 0.6% technical grade (96% pure) compound for 96 weeks (Tsuda et al., 1982). The mice were observed for the following 8 weeks at which time they were sacrificed for histological examinations of all organs (not specified). Mice that died or became moribund during the experiment were also examined, but only those mice surviving >52 weeks (the time at which the first liver tumor was found in an animal that subsequently died) were used for tabulation of lesion incidences (i.e., effective numbers). It should be noted that the basis for the selection of the exposure levels used in this study was not indicated.

There were no treatment-related differences in the food consumption of either sex, but dose-related decreases in mean body weight were reported for both females (after week 72) and males (Tsuda et al., 1982). Survival was decreased significantly in all treated mice during the later stages of the experiment (after ~80 weeks in the males and 72 weeks in the females), but the response was clearly dose-related only in the females. Terminal (week 104) survival was approximately (interpolated from survival curves) 72, 55, 30 and 17% (males) and 74, 50, 10 and 0% (females) in the control, 0.15, 0.3 and 0.6% dose groups, respectively. It should be noted that the main cause of death was massive intraperitoneal hemorrhage, which was due to the rupture of liver tumors, and that all of the female mice in the 0.6% treatment group died before the end of the experiment (approximately week 100).

Statistically significant increased incidences of neoplastic lesions were found in the liver and forestomach of all treated groups. As detailed in Table 5-1, the occurrence of hepatocellular carcinomas was dose-related in the male mice. The occurrence of hepatocellular carcinoma in females was not dose-related, but the incidences in all of the treated groups were significantly higher than in the control group. The incidences of neoplastic nodules in the liver were significantly increased in all treatment groups of both sexes, except the high-dose males, but the responses were not dose-related. The overall incidence of hepatocellular carcinoma metastases (all sites) was reported to be increased significantly in males treated with 0.3% carbazole and in females at all dose levels (data not reported), but incidences of metastases to the lungs (the primary site of metastases) were not increased significantly (see Table 5-1). In the forestomach, the incidence of papillomas was significantly higher in all groups of females and the high-dose group of males than it was in the controls. Squamous cell carcinoma of the forestomach showing invasion to the submucosal layer was significantly increased in the high-dose male mice. The incidences of tumors in tissues other than the liver and forestomach were not significantly different from controls in any of the three treatment groups in either sex.

Shear and Leiter (1941) administered six subcutaneous injections of crystallized carbazole, moistened with glycerol, into the left flanks of a group of 10, 3- to 4-month-old male strain A mice. The injections totaled ~60 mg, but individual injection quantities, body weights and the schedule of administration were not specified. All 10 mice were alive after 12 months, 7 were alive after 15 months and 4 were alive at 19 months (the end of the study). Injection site tumors were not observed in any of the

TABLE 5-1

Incidence of Tumors in B6C3F1 Mice Administered Technical Grade (96% Pure) Carbazole in the Diet for 96 Weeks and Examined After 104 Weeks[a]

Sex	Concentration in Diet (%)	Target Organ	Tumor Type	Tumor Incidence[b] (p value)
Male	0	liver	neoplastic nodules	13/46
	0.15			30/42 (p<0.001)
	0.3			22/42 (p<0.05)
	0.6			10/48 (NS)
	0	liver	hepatocellular carcinoma	9/46
	0.15			12/42 (NS)
	0.3			20/42 (p<0.01)
	0.6			37/48 (p<0.001)
	0	lung	metastases[c]	2/46
	0.15			2/42 (NS)
	0.3			7/42 (NS)
	0.6			11/48 (p<0.01)
Female	0	liver	neoplastic nodules	2/45
	0.15			13/49 (p<0.01)
	0.3			21/43 (p<0.001)
	0.6			16/46 (p<0.001)
	0	liver	hepatocellular carcinoma	2/45
	0.15			35/49 (p<0.001)
	0.3			24/43 (p<0.001)
	0.6			30/46 (p<0.001)
	0	lung	metastases[c]	0/45
	0.15			5/49 (NS)
	0.3			3/43 (NS)
	0.6			3/46 (NS)

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TABLE 5-1 (cont.)

Sex	Concentration in Diet (%)	Target Organ	Tumor Type	Tumor Incidence[b] (p value)
Male	0	forestomach	papilloma	0/46
	0.15			0/42 (NS)
	0.3			1/42 (NS)
	0.6			4/48 (p<0.05)
	0	forestomach	squamous cell carcinoma	0/46
	0.15			0/42 (NS)
	0.3			0/42 (NS)
	0.6			7/48 (p<0.01)
Female	0	forestomach	papilloma	0/45
	0.15			5/49 (p<0.05)
	0.3			7/43 (p<0.01)
	0.6			4/46 (p<0.05)
	0	forestomach	squamous cell carcinoma	0/45
	0.15			0/49 (NS)
	0.3			1/43 (NS)
	0.6			2/46 (NS)

[a]Source: Tsuda et al., 1982

[b]Number of tumor-bearing mice (number of mice examined)

[c]Hepatocellular carcinoma metastases. Overall incidence of metastases (all sites) was reported to be significantly increased in mid-dose males and in females at all doses, but the study was ambiguous and data were not reported.

NS = Not significant

treated animals. Additional information regarding the design or results of this experiment, which was part of a survey of polcyclic compounds, was not reported.

The results of inadequately reported skin application experiments were published in the early literature. Kennaway (1924) reported that unspecified application of 1% carbazole in alcohol to 100 mice of unspecified strain for 9 months had "no effects upon the skin or bladder." Application of carbazole to the skin of 30 mice for ~2 years produced a skin tumor (an ulcerating tumor with basal infiltration) in one animal (Maisin et al., 1927). The dosage and application schedule used in this study were not specified, but it was reported that benzene was used as the vehicle during the first months (number not specified) and that lanolin was subsequently used. IARC (1983) reported the results of a German study (Shear and Leiter, 1941) in which a solution of 0.5% carbazole in benzene was applied 120 times to the skin of 50 mice. Additional experimental details were not summarized, but the only reaction observed after 276 days was epilation of the application site.

5.2. MUTAGENICITY

The experimental design and results of mutagenicity assays of carbazole are summarized in Table 5-2. Bacterial test systems were used in all of the studies, and the only assay that was conducted in multiple studies was the Ames Salmonella typhimurium reverse mutation assay.

Most of Ames assays showed that carbazole was not mutagenic to S. typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 when tested in plate incorporation tests with or without S-9 metabolic activation preparation (Florin et al., 1980; Salamone et al., 1979; Anderson and Styles, 1978; Epler et al., 1979; LaVoie et al., 1982; Bechtold et al., 1985; Hasegawa et al., 1985). Equivocal results were obtained in one plate incorporation

TABLE 5-2

Mutagenicity Testing of Carbazole

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1535 TA1537 TA98 TA100	>97%	spot test	3 µmol/ plate	±S-9 (rat, Aroclor)	 ± ± ± ±	unspecified equivocal results in spot tests prompted quantitative plate incorporation assay (see below)	Florin et al., 1980
	S. typhimurium TA1535 TA1537 TA100	>97%	plate incorporation	0.03, 0.3, 3 and 30 µmol/ plate	±S-9 (rat, Aroclor)	 - - -	Precipitated at 30 µmol/ plate	Florin et al., 1980
	S. typhimurium TA1535 TA1537 TA1538 TA98 TA100	NR	plate incorporation	0.1-1000 µg/plate	±S-9 (rat, Aroclor)	 - - - - -	No comment	Salamone et al., 1979
	S. typhimurium TA1535 TA1538 TA98 TA100	NR	plate incorporation	4, 20, 100, 500 and 2500 µg/plate	±S-9 (rat, Aroclor)	 - - - -	No comment	Anderson and Styles, 1978
	S. typhimurium TA100	NR	plate incorporation	NR	±S-9 (rat, Aroclor)	 -	Assay conducted over at least a 1000-fold concentration range	Epler et al., 1979
	S. typhimurium TA1535 TA1537 TA1538 TA98 TA100	purified	plate incorporation	5, 10, 25, 50, 100 and 250 µg/ plate	±S-9 (rat, Aroclor)	 - - - - -	Similar assays of 16 carbazole derivatives showed that mutagenic activity is associated only with a 9-methyl substituent	LaVoie et al., 1982

TABLE 5-2 (cont.)

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Reverse mutation	S. typhimurium TA98	NR	plate incorporation	50, 100 or 200 µg/ plate	±S-9 (rat, Aroclor)	-	No comment	Bechtold et al., 1985
	S. typhimurium TA98	NR	plate incorporation	10, 50, 100, 250 or 500 µg/plate	±S-9 (rat, Aroclor)	±	Reversion frequencies approximately twice the solvent control at doses >50 µg/plate, but response not clearly dose-related	Ho et al., 1981
	S. typhimurium TA98 TA100	NR	NR	NR	NR	- -	No comment	Hasegawa et al., 1985
	Escherichia coli Sd-4-73	NR	spot test	1 microdrop (0.01-0.025 ml); concentration NR	none	-	Reversion from streptomycin dependence to independence scored	Szybalski, 1958
Forward mutation	S. typhimurium TM677	NR	liquid suspension	≤3 mM	±S-9 (rat, Aroclor and phenobarbital)	-	Induction of resistence to 8-azaguanine scored. Highest concentration tested was the upper limit of solubility and was the only one listed	Kaden et al., 1979
Growth Inhibition	Bacillus subtilis	NR	NR	NR	NR	-	'Rec assay'	Hasegawa et al., 1985
Chromosome Aberration	Chinese hamster fibroblasts (cell line CHF)	NR	NR	NR	NR	+	Results noted as an addendum to a carcinogenicity bioassay	Isuda et al., 1982

NR = Not reported

assay conducted with one strain (TA98) of S. typhimurium (Ho et al., 1981), but concentrations were comparable to those used in the negative assays with TA98 (see Table 5-2). A qualitative spot test was conducted with strains TA1535, TA1537, TA98 and TA100 in one study with equivocal results (Florin et al., 1980), but subsequent testing with three of these strains in plate incorporation assays in the same study was negative. Reverse mutation testing with Escherichia coli Sd-4-73 (Szybalski, 1958; and forward mutation testing with S. typhimurium TM 677 (Kaden et al., 1979) were negative. It is indicated in the abstract of a Japanese study (Hasegawa et al., 1985) that carbazole was not differentially toxic to wild-type or DNA repair-deficient strains of Bacillus subtilis.

Extremely limited information is available regarding the clastogenic potential of carbazole. Tsuda et al. (1982) noted in an addendum to a carcinogenicity bioassay that carbazole caused chromosomal aberrations in the Chinese hamster fibroblast cell line CHF. Additional information regarding this study was not reported.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of carbazole could not be located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of carbazole could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Limited information is available regarding nonneoplastic effects of chronic exposure to carbazole. In the oral carcinogenicity bioassay detailed in Section 5.1., groups of 50 male and 50 female B6C3F1 mice were fed diets containing 0, 0.15, 0.3 or 0.6% carbazole for 96 weeks and observed

for an additional 8 weeks (Tsuda et al., 1982). Although food consumption in either sex was not affected by treatment, dose-related decreases in body weight reportedly occurred (data not provided) in the males throughout the study and in the females after week 72; from weeks 40-72 the body weights of females in the 0.15% treatment group were higher than the controls. Survival was markedly affected by treatment during the later stages of the experiment (see Section 5.1.), but the main cause of death was hemorrhage, which was due to the rupture of liver tumors (other causes were not discussed).

5.6. OTHER RELEVANT INFORMATION

An oral LD_{50} of >5000 mg/kg has been reported for male albino Wistar rats (Eagle and Carlson, 1950).

A single topical application of carbazole at a dose of 100 mg/kg resulted in significantly ($p<0.05$) increased activities of aryl hydrocarbon hydroxylase and O-deethylase in the skin and liver of neonatal rats (Mukhtar et al., 1982).

Addition of 1 mM carbazole to a suspension of mouse ascites sarcoma BP8 cells caused slight (8%) inhibition of growth rate (Pilotti et al., 1975).

5.7. SUMMARY

Dietary administration of 96% pure carbazole B6C3F1 mice at concentrations of 0.15, 0.3 and 0.6% for 96 weeks produced neoplasms in the liver and forestomach (Tsuda et al., 1982). Lesions that occurred with significantly increased frequencies included neoplastic nodules in the liver (all groups except high-dose males), hepatocellular carcinoma (all groups except low dose males), papillomas of the forestomach (all groups except low- and middle-dose males) and squamous cell carcinoma of the forestomach (high dose males only). Metastasis from the liver to the lung was significantly

($p<0.01$) noted in the high-dose group and with marginal significance in the medium-dose group. Six subcutaneous injections of carbazole that totaled ~60 mg did not produce local tumors in 10 male strain A mice after 12-19 months, but the individual doses and schedule of administration were not reported (Shear and Leiter, 1941). The results of inadequately reported skin application studies with mice do not indicate a local tumorigenic effect of carbazole (Kennaway, 1924; Maisin et al., 1927; Shear and Leiter, 1941).

Carbazole has been reported to be nonmutagenic in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and/or TA100 when tested in plate incorporation assays with or without S-9 metabolic activation (Florin et al., 1980; Salamone et al., 1979; Anderson and Styles, 1978; Epler et al., 1979; LaVoie et al., 1982; Bechtold et al., 1985; Hasegawa et al., 1985). Equivocal results were obtained by one investigator (Ho et al., 1981) in a plate incorporation assay with strain TA98 conducted with or without S-9 at concentrations comparable to the negative studies. Equivocal results were also obtained in Ames spot tests with four strains of S. typhimurium with or without S-9 (Florin et al., 1980), but these findings were not substantiated in plate assays in the same study. Carbazole was not active in a reverse mutation assay with E. coli Sd-4-73 without S-9 (Szybalski, 1958) or in a forward mutation assay with S. typhimurium TM 677 with or without S-9 (Kaden et al., 1979). Inadequate reports indicate that carbazole was not differentially toxic to wild or DNA-repair deficient strains of B. subtilis (Hasegawa et al., 1985), but did induce chromosomal aberrations in cultured Chinese hamster fibroblasts (Tsuda et al., 1982).

Information regarding the chronic toxic effects unrelated to carcinogenesis, subchronic toxicity, teratogenicity or other reproductive effects could not be located in the available literature as cited in the Appendix.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Applegate et al. (1957) reported that when rainbow trout, Salmo gairdneri, or bluegills, Lepomis macrochirus were exposed to 5 mg/ℓ carbazole, the average time to death or distress was 5 and 13 hours, respectively. Thomas et al. (1981) conducted a series of tests of lethal and sublethal effects of carbazole on striped mullet, Mugil cephalus, and found that a concentration of 1 mg/ℓ caused 100% mortality in 3 days. Fish exposed to 0.1 mg/ℓ exhibited no differences from controls in terms of their corticosteroid hormone response to handling stress. Moderate hyperglycemia occurred in fish exposed to 0.01 or 0.1 mg/ℓ, but after 1 week this effect was significant only in fish exposed to 0.1 mg/ℓ. Plasma cortisol levels were significantly elevated in fish exposed to 0.01 mg/ℓ, but not in fish exposed to 0.1 mg/ℓ. Fish exposed to 1 or 5 mg/ℓ were paralyzed or moribund after 1 day.

The 60- and 72-hour EC_{50} for inhibition of population growth of the ciliate Tetrahymena pyriformis, was reported to be 0.12 mmol/ℓ (20 mg/ℓ) (Schultz, 1983; Schultz et al., 1980).

6.2. PLANT EFFECTS

Pertinent data concerning the toxicity of carbazole to aquatic plants could not be located in the available literature as cited in the Appendix.

6.3. RESIDUES

Pertinent data concerning concentrations of carbazole in aquatic organisms could not be located in the available literature as cited in the Appendix. Carbazole injected into the caudal vein of English sole, Parophrys vetulus, was metabolized to carbazole-9-oxyl in the liver. This might be related to formation of hepatic lesions and other neoplasms (Roubal and Malins, 1985).

6.4. SUMMARY

Little information is available regarding the toxicity of carbazole to aquatic organisms. Concentrations of $\geq$1 mg/ℓ were acutely lethal to the saltwater fish, Mugil cephalus, while concentrations $\leq$0.1 mg/ℓ were tolerated for 1 week (Thomas et al., 1981). A concentration of 5 mg/ℓ was lethal to the freshwater fishes, Salmo gairdneri and Lepomis macrochirus (Applegate et al., 1957).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature as cited in the Appendix.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of carbazole could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

In the only chronic study available using a relevant route of exposure, carbazole was administered to groups of 50 male and 50 female B6C3F1 mice in the diet at concentrations of 0, 0.15, 0.3 or 0.6% for 96 weeks (Tsuda et al., 1982). As detailed in Section 5.1., histopathological examination after 96 weeks of dietary exposure to carbazole plus 8 weeks of observation showed statistically significant increases in the incidences of neoplastic nodules in the liver and hepatocellular carcinomas as well as papillomas of the forestomach in most treatment groups of both sexes. The incidence of squamous cell carcinoma of the forestomach was increased significantly in the high-dose males, but not in any of the female groups. Additionally, it appears that the overall incidence of hepatocellular carcinoma metastases (all sites) was significantly increased in the 0.3% males and in females at all doses.

Injection site tumors did not develop in a group of 10 male strain A mice that were administered six subcutaneous injections of carbazole that totaled ~60 mg (Shear and Leiter, 1941). The individual dosages and schedule of administration were not specified, but survival was 100% after 12 months and 40% after 19 months (the end of the study). Inadequately reported skin painting studies with mice also do not indicate a local tumorigenic effect of carbazole. Kennaway (1924) reported that unspecified application of 1% carbazole to 100 mice for 9 months had no effect (presumably tumorigenic) on the skin or bladder. Unspecified application of an unreported amount of carbazole to the skin for ~2 years produced one tumor (an ulcerative lesion with basal infiltration) in 1/30 mice (Maisin et

al., 1927). Shear and Leiter (1941) applied 0.5% carbazole 120 times (quantity and schedule not specified) to the skin of 50 mice and found no local tumors after 276 days.

Carbazole has been reported to be nonmutagenic in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and/or TA100 when tested in plate incorporation assays with and without S-9 metabolic activation (Florin et al., 1980; Salamone et al., 1979; Anderson and Styles, 1978; Epler et al., 1979; LaVoie et al., 1982; Bechtold et al., 1985; Hasegawa et al., 1985). Equivocal results were obtained in an Ames spot test with strains TA1535, TA1537, TA98 and TA100 (Florin et al., 1980) but these findings were not substantiated in plate assays in the same study. Equivocal results were also obtained in a plate incorporation assay with strain TA98 in one study (Ho et al., 1981), but all of the negative assays that were conducted with TA98 (Florin et al., 1980; Salamone et al., 1979; Anderson and Styles, 1978; LaVoie et al., 1982; Bechtold et al., 1985) were tested in the same concentration range. Carbazole was not mutagenic in a reverse mutation assay with Escherichia coli Sd-4-73 without S-9 activation (Szybalski, 1958) or in a forward mutation assay with S. typhimurium TM677 with or without S-9 (Kaden et al., 1979). It has also been reported that carbazole was not differentially toxic to wild or DNA-repair deficient strains of Bacillus subtilis (activation not specified) (Hasegawa et al., 1985). Tsuda et al. (1982) noted in an addendum to a carcinogenicity study that carbazole produced chromosomal aberrations in cultured Chinese hamster fibroblasts. An explanation for the discrepancy between the observed carcinogenicity of carbazole and the predominately negative mutagenicity data is not clear, but may be related to differences in its in vivo and in vitro metabolism.

Pertinent data regarding the nonneoplastic effects of chronic or subchronic exposure to carbazole, or information regarding teratogenic and reproductive effects of carbazole could not be located in the available literature as cited in the Appendix. Treatment-related mortality occurred in mice of both sexes in the oral carcinogenicity study by Tsuda et al. (1982), but this was attributed to hepatocellular carcinoma development. Reduced body weight gain with normal food consumption also occurred, but body weight data were not reported and this effect is probably also secondary to the neoplasia.

Since chronic dietary administration of carbazole was shown to be carcinogenic to mice (Tsuda et al., 1982), it is appropriate to derive a q_1^*. The hepatocellular carcinoma response was stronger than the forestomach squamous cell carcinoma response, and the occurrence of hepatocellular carcinoma is most clearly related to dose in the male mice. Using the tumor incidences for hepatocellular carcinoma in the male mice and the data presented in Table 8-1, an unadjusted q_1^* of 1.5654×10^{-3} $(mg/kg/day)^{-1}$ was calculated using the computerized multistage model developed by Howe and Crump (1982). The dietary exposures of 0, 0.15, 0.3 and 0.6% were equivalent to cumulative doses of 0, 153.0, 366.4 and 747.1 g/kg bw for females and 0, 139.8, 290.0 and 628.3 g/kg bw for males (Tsuda et al., 1982). Dividing the cumulative doses by the number of days in the study results in daily doses of 0, 210.2, 503.3 and 1067 mg/kg/day for females and 0, 192.0, 398.4 and 863.0 mg/kg/day for males. The number of days in the study was 728 (7 days/week x 104 weeks) except for the high-dose females. All high-dose females died within 100 weeks; therefore, the number of days for this group was 700. The unadjusted q_1^* is converted to a q_1^* for humans by multiplying by the cube root of the ratio of the body weight of humans

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: Carbazole

Reference: Tsuda et al., 1982

Species, Strain, Sex: Mouse, B6C3F1, male

Body weight: 0.03 kg (assumed)

Length of exposure (le) = 96 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: liver, hepatocellular carcinoma

Route, vehicle: oral, diet

Experimental Doses or Exposures (%)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	9/46
0.15	192.0	12/42
0.3	398.4	20/42
0.6	863.0	37/48

Unadjusted q_1^* from study = 1.5654×10^{-3} $(mg/kg/day)^{-1}$

Human q_1^* = 2.0762×10^{-2} $(mg/kg/day)^{-1}$

(assumed 70 kg) to the body weight of mice (assumed 0.03 kg); adjustment for lifespan is unnecessary because the assumed lifespan of the animals is the same as the duration of the experiment (2 years). The resultant q_1^* is 2.08×10^{-2} $(mg/kg/day)^{-1}$.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Limited information regarding nonneoplastic effects of chronic exposure to carbazole is provided in a carcinogenicity bioassay (Tsuda et al., 1982). In this study, carbazole was administered to groups of 50 male and 50 female B6C3F1 mice at concentrations of 0, 0.15, 0.3 and 0.6% in the diet for 96 weeks. Comprehensive histological examinations were conducted after 8 weeks without exposure, but results regarding nonproliferative lesions were not reported. Weight loss, food consumption and mortality were the only nonneoplastic endpoints discussed in the study. Dose-related reductions in mean body weight were observed in both the male and female mice. Although data were not reported, the dose response in females reportedly was clear only after week 72 (from weeks 40-72 the body weights of the 0.15% females were higher than the controls). Food consumption in the treated groups did not differ significantly from control levels in either sex (data reported). Treatment-related mortality occurred in both sexes, with terminal (week 104) survival rates of ~72, 55, 30 and 17% in males and 74, 50, 10 and 0% in females in the control, 0.15, 0.3 and 0.6% dose groups, respectively. It should be noted, however, that the main cause of death was massive intraperitoneal hemorrhage, which was due to the rupture of liver tumors. Therefore, since mortality is related to tumor development, it cannot be used to calculate an MED for use in derivation of an RQ based on chronic toxicity. Weight loss also appears to be an inappropriate endpoint for MED calculation since it is reasonable to infer that this effect is also secondary to carcinogenesis. Therefore, data are not sufficient for deriving an RQ for carbazole (Table 9-1).

TABLE 9-1

Carbazole

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:

Dose:

Effect:

Reference:

RV_d:

RV_e:

Composite Score:

RQ: Data are not sufficient for deriving an RQ.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Carbazole has been shown to be carcinogenic when administered orally to B6C3F1 mice of both sexes (Tsuda et al., 1982). As detailed in Table 5-1, administration of carbazole in the diet at concentrations of 0.15, 0.3 and 0.6% produced significantly increased incidences of hepatocellular carcinoma in all but the low-dose males, and significantly increased incidences of forestomach squamous cell carcinoma in the high-dose males. In addition, significantly increased incidences of related proliferative lesions (neoplastic nodules in the liver, papillomas in the forestomach) occurred in many of the treatment groups.

Six subcutaneous injections of carbazole that totaled ~60 mg did not induce local tumors in a group of 10 male strain A mice that survived at least 12 months (Shear and Leiter, 1941). Individual dosages and the schedule of administration, however, were not specified. Unspecified application of 1% carbazole to the skin of 100 mice for 9 months had "no effect upon the skin or bladder" (Kennaway, 1924). In another dermal study, unspecified application of carbazole for ~2 years produced a local tumor (ulcerating with basal infiltration) in 1/30 mice (Maisin et al., 1927). Applications of 0.5% carbazole 120 times (schedule not specified) to the skin of 50 mice did not produce application site tumors after 276 days (Shear and Leiter, 1941). Although negative, the above studies, because of inadequate reporting and limited experimental design, are inadequate for evaluation of carcinogenicity.

The available evidence for carcinogenicity (Tsuda et al., 1982) indicates that it is appropriate to classify carbazole as an EPA category C chemical (i.e., carcinogenicity was demonstrated in a single experiment using a single species and strain). Category C is interpreted to mean

carbazole is a possible human carcinogen (U.S. EPA, 1984). A potency factor (unadjusted $1/ED_{10}$) for carbazole was calculated from the dose-response data for hepatocellular carcinoma in male mice (Table 9-2) using the computerized multi-stage model developed by Howe and Crump (1982). The transformed doses were calculated by dividing the average cumulative doses (expressed as g/kg bw) that were provided by Tsuda et al. (1982) by the number of days in the study (7 days/week x 104 weeks = 728 days). The F factor for humans was calculated by multiplying the unadjusted $1/ED_{10}$ by the cube root of the ratio of human weight (assumed 70 kg) to the weight of the mice (assumed 0.03 kg). The resultant F factor of 9.23×10^{-2} $(mg/kg/day)^{-1}$ is <1, indicating that carbazole should be placed in potency group 4. A potency group 4 and an IARC group 2B and EPA Group C (U.S. EPA. 1984) chemical has a LOW hazard ranking under CERCLA guidelines.

TABLE 9-2

Derivation of Potency Factor (F)
Agent: Carbazole

Reference:	Tsuda et al., 1982			
Exposure route:	oral			
Species:	mouse			
Strain:	B6C3F1			
Sex:	male			
Vehicle or physical state:	diet			
Body weight:	0.03 kg (assumed)			
Duration of treatment:	96 weeks			
Duration of study:	104 weeks			
Lifespan of animal:	104 weeks			
Target organ:	liver			
Tumor type:	hepatocellular carcinoma			
Experimental doses/ exposure:	0%	0.15%	0.3%	0.6%
Transformed doses (mg/kg/day):	0	180	360	720
Tumor incidence:	9/46	12/42	20/42	37/48
Unadjusted $1/ED_{10}$:	6.9610×10^{-3}			
$1/ED_{10}$ (F factor):	9.2328×10^{-2}			

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN Internation
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in August, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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